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The Impact of Parkinson's Disease on the Cortical Mechanisms That Support Auditory–Motor Integration for Voice Control

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Abstract: Several studies have shown sensorimotor deficits in speech processing in individuals with idiopathic Parkinson's disease (PD). The underlying neural mechanisms, however, remain poorly understood. In the present event-related potential (ERP) study, 18 individuals with PD and 18 healthy controls were exposed to frequency-altered feedback (FAF) while producing a sustained vowel and listening to the playback of their own voice. Behavioral results revealed that individuals with PD produced significantly larger vocal compensation for pitch feedback errors than healthy controls, and exhibited a significant positive correlation between the magnitude of their vocal responses and the variability of their unaltered vocal pitch. At the cortical level, larger P2 responses were observed for individuals with PD compared with healthy controls during active vocalization due to left-lateralized enhanced activity in the superior and inferior frontal gyrus, premotor cortex, inferior parietal lobule, and superior temporal gyrus. These two groups did not differ, however, when they passively listened

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to the playback of their own voice. Individuals with PD also exhibited larger P2 responses during active vocalization when compared with passive listening due to enhanced activity in the inferior frontal gyrus, precental gyrus, postcentral gyrus, and middle temporal gyrus. This enhancement effect, however, was not observed for healthy controls. These findings provide neural evidence for the abnormal auditory–vocal integration for voice control in individuals with PD, which may be caused by their deficits in the detection and correction of errors in voice auditory feedback. *Hum Brain Mapp 37:4248–4261, 2016*.

Key words: auditory feedback; Parkinson's disease; auditory–vocal integration; event-related potentials; sLORETA

INTRODUCTION

Idiopathic Parkinson's disease (PD) is a neurodegenerative disease caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia (BG). The worldwide prevalence of PD ranges from 41 in 100,000 people who are 40–49 years of age, to 1,903 in 100,000 in people over 80 years [Pringsheim et al., 2014]. Although the central symptoms of PD include resting tremor, bradykinesia, and rigidity [Tolosa et al., 2006], 70%–90% of individuals with PD develop motor speech disorders during the course of the disease [Sapir et al., 2008]. The speech motor symptoms of PD can include hypophonia, hypoprosodia, poor enunciation of consonants and vowels, festination or hesitation of speech, and voice tremor [Duffy, 2005]. Understanding how PD affects the neural systems that support vocal production may lead to new approaches to diagnosis and therapies for these speech deficits. To date, however, it is unclear how PD alters these functional neural mechanisms to cause motor speech disorders.

Several studies have suggested that while speaking, individuals with PD do not perceive the sound of their own voice in the same way as healthy individuals. For example, individuals with PD often complain that they are speaking too loudly when they are asked to increase what others perceive as their soft speech, to a normal conversation level [Fox and Ramig, 1997]. Similarly, in a study by Ho et al. [2000], individuals with PD who spoke with a softer voice perceived their own voice to be louder than healthy controls, and they overestimated the loudness of their speech during both reading and conversation. When individuals with PD hear a tape recording of themselves using increased loudness, however, they can easily recognize that their voice sounds within normal limits, despite their feelings of talking too loudly during the time of the recording [Fox et al., 2002]. These findings suggest that receptive listening is not impaired in individuals with PD; however, they may have dysfunctions in the processing of their online sensory feedback (auditory and/or proprioceptive) while speaking.

The BG are connected to cortical and subcortical regions that play a major role in the processing and gating of sensorimotor information, and in the regulation of muscle tone and smoothness of movements [Boecker et al., 1999; Maschke et al., 2003]. Behavioral evidence indicates that the loss of dopaminergic neurons in the BG compromises the sensorimotor control of speech. For example, individuals with PD exhibit abnormal laryngeal somatosensory function, characterized by decreased subglottal air pressure, peak air flow, laryngeal resistance, lung air volume expended for each syllable, slope of declination in air flow, voice intensity, and vocal onset latencies compared with healthy controls [Hammer and Barlow, 2010]. When exposed to altered auditory feedback during speech, individuals with PD exhibit abnormal integration of the auditory and vocal motor systems for voice control [Chen et al., 2013a; Kiran and Larson, 2001; Liu et al., 2012; Mollaei et al., 2013]. For example, when healthy speakers hear their vocal pitch briefly shifted downward or upward, they rapidly and automatically shift their vocal pitch in the opposite direction of the pitch shift they hear [Burnett et al., 1998; Chen et al., 2007; Jones and Munhall, 2002]. Although individuals with PD, when on their medication, have been shown to similarly compensate for the frequency-altered auditory feedback (FAF), their vocal response peak and end times were significantly longer than healthy controls [Kiran and Larson, 2001]. By asking individuals with PD to be off medication at least 12 hours prior to testing, both Liu et al. [2012] and Chen et al. [2013a] found that individuals with PD produced significantly larger vocal compensations than healthy controls when they heard their auditory feedback suddenly shifted in pitch or loudness. Moreover, these larger vocal compensations were positively correlated with increased variability in the production of unaltered voice fundamental frequency (F_0) in individuals with PD, but not in healthy controls [Chen et al., 2013a], suggesting that individuals with PD appear to rely more on auditory feedback during their speech production. In addition, Mollaei et al. [2013] found that individuals with PD showed less sensorimotor learning than healthy controls when they heard the first formant frequency of the vowel/ɛ/shifted 30% upward when they said the word "head" (/hɛd/), indicating that they are less able to use auditory feedback to update their feedforward control. Together, these studies suggest that

sensorimotor deficits in speech observed in individuals with PD are most likely related to dysfunctions in the integration of auditory and/or somatosensory information into the vocal motor systems during ongoing speech.

To date, few studies have been conducted to investigate how PD affects the neural substrates involved in speech motor control. In two studies measuring regional cerebral blood flow (rCBF) with positron emission tomography (PET), individuals with PD exhibited increased blood flow in the premotor cortex (PMC), supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), as well as the sensory regions such as superior temporal gryus (STG) and inferior parietal lobule (IPL), during speech production tasks relative to healthy controls [Liotti et al., 2003; Pinto et al., 2004]. Following successful voice therapy, individuals with PD have exhibited a right-sided functional reorganization of brain activation in the areas of DLFPC, PMC, and auditory cortices during speech production [Liotti et al., 2003; Narayana et al., 2010]. In two functional magnetic resonance imaging (fMRI) studies, compared with healthy controls, individuals with PD showed increased functional connectivity of periaqueductal gray matter (PAG) to the right BG, posterior STG, supramarginal and fusiform gyri, and IPL [Rektorova et al., 2012] and over-activated the left dorsal PMC, inferior frontal gyrus (IFG), and auditory cortex [Arnold et al., 2014] during overt speech. In another fMRI study examining the resting-state vocalization network, individuals with PD exhibited significantly reduced left thalamus, putamen, STG, and Rolandic operculum (RO) connectivity than healthy controls [New et al., 2015].

Although behavioral work has shown that sensorimotor deficits in speech processing are symptoms of PD, much less is known about the neural correlates of the deficits in feedback-based monitoring of vocal production that are associated with PD. Furthermore, previous research primarily investigated the behavioral performance and/or neural substrates associated with actively producing speech, whereas passively listening to the playback of self-produced speech was not included as a condition. Without comparing active vocalization to passive listening, it is difficult to determine whether previous observations were the result of PD's effect on the sensory mechanisms alone, or whether the effect is the result of the interaction between the sensory and motor systems. Considerable evidence from both animals and humans has demonstrated that when auditory feedback is either unaltered or altered at utterance onset, cortical responses to self-produced vocalizations are suppressed relative to passive listening [Behroozmand and Larson, 2011; Eliades and Wang, 2003; Heinks-Maldonado et al., 2005; Houde et al., 2002]. Cortical responses, however, are larger for active vocalizations as compared with passive listening when voice auditory feedback is altered in the middle of an utterance [Behroozmand et al., 2009; Chang et al., 2013; Chen et al., 2013b; Eliades and Wang, 2008], and the size of cortical response in the auditory and motor regions is predictive of the magnitude of vocal compensation for voice feedback errors [Behroozmand et al., 2015; Chang et al., 2013]. It has been suggested that vocalization-induced suppression enables speakers to distinguish self-produced speech from externally generated sounds while vocalization-induced enhancement allows them to detect mismatches between intended and actual auditory feedback for online control of vocal production [Chang et al., 2013].

The present study used event-related potentials (ERP) in combination with standard low-resolution electromagnetic tomography (sLORETA) to determine the spatio-temporal pattern of brain activity during auditory-motor integration for voice control in individuals with PD. Individuals with PD and healthy controls were exposed to FAF regarding their ongoing vocalizations while they sustained a vowel phonation. Later, they passively listened to these same vocal utterances that were recorded under the FAF condition. The magnitudes and latencies of vocal responses and N1 and P2 ERP components [Chen et al., 2012; Hawco et al., 2009] were compared across conditions. Based on previous findings [Chen et al., 2013a; Liu et al., 2012], we hypothesized that individuals with PD would produce significantly larger vocal compensations for pitch-shifted auditory feedback than healthy controls. Previous research has also shown that active vocalization elicits significantly larger P2 responses than passive listening [Behroozmand et al., 2009, 2011; Chen et al., 2013b], so we expected this vocalization-induced enhancement to be observed in individuals with PD and healthy controls. Finally, because individuals with PD tend to overestimate their vocal effort even though they can accurately assess the vocal loudness of their own speech and the speech of others in recordings [Fox et al., 2002; Ho et al., 2000], we hypothesized that individuals with PD would produce significantly larger N1 and/or P2 responses than healthy controls during active vocalization, but this difference would not exist during passive listening.

MATERIALS AND METHODS

Subjects

Eighteen individuals (13 males and 5 females; 66.4 ± 11.1 years), who were diagnosed as having idiopathic PD, participated in the present study. All the participants with PD were native speakers of Cantonese Chinese, a dialect that is spoken in Southern China and other Chinese communities. The mean disease duration since the appearance of movement symptoms was 4.7 (SD: 3.5) years. The mean Hoehn and Yarh stage was 2.2 (SD: 0.6), ranging from 1 to 3. Although individuals with PD had complaints about speech abnormalities such as hypophonia, hypoprosodia, and poor voice quality, none of them received speech treatment prior to testing. The non-speech performance was evaluated using the Unified Parkinson's

Disease Rating Scale (UPDRS-III) [Fahn et al., 1987]. The mean score was 23.6 (SD: 9.6) and ranged from 7 to 41 in their off-medication state. All individuals with PD were on anti-PD medication, including L-levodopa and/or another dopaminergic or anticholinergic medication, but they were tested in their off-medication state (12 hours off anti-PD medication). Eighteen age-, sex-, language-, and education-matched healthy controls (13 males and 5 females; 66.4 ± 11.2 years) were recruited for the present study. These healthy controls had no history of speech, language, or neurological disorders. Both the individuals with PD and the healthy controls passed a binaural hearing screening and had thresholds of 40 dB hearing level (HL) or less for 500, 1,000, 2,000, and 4,000 Hz. Written informed consent was obtained from all participants, and the research protocol was approved by the Institutional Review Board of The First Affiliated Hospital at Sun Yat-sen University of China in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Procedure

The experiment consisted of one block of active vocalization and one block of passive listening. During active vocalization, all participants sustained a phonation of the vowel sound/u/for about 5–6 s at their comfortable level. During each vocalization, their voice feedback was unexpectedly pitch-shifted downward 200 cents (100 cents equals 1 semitone) four times. The duration of each pitch shift lasted for 200 ms. The first pitch shift occurred 500–1,000 ms after the vocal onset, and the succeeding pitch shifts were presented with an inter-stimulus interval of 700–900 ms. Participants were required to take a pause of 2–3 s between successive vocalizations to avoid the vocal fatigue. Participants produced 25 consecutive vocalizations, resulting in a total of 100 trials. The block of active vocalization was followed by one block of passive listening, during which participants passively listened to a recording of their pitch-shifted voice.

Apparatus

Subjects were seated in a sound-treated booth throughout the experiment. In order to partially mask the airborne and bone-conducted feedback, we calibrated the experimental system so that the intensity of voice feedback was 10 dB sound pressure level (SPL) higher than that of subject's vocal output [Behroozmand et al., 2009]. The voice signals were transduced through a dynamic microphone (DM2200, Takstar Inc.), amplified with a MOTU Ultralite Mk3 Firewire audio interface, and pitch-shifted through an Eventide Eclipse Harmonizer. A custom-developed MIDI software program (Max/MSP v.5.0 by Cycling 74) running on an iMac was used to control the Eventide Eclipse Harmonizer to pitch-shift the voice feedback. Finally, the voice signals were amplified by an ICON NeoAmp headphone amplifier and fed back to participants through insert earphones (ER1-14A, Etymotic Research Inc.).

After the block of active vocalization, the recorded pitch-shifted voice was played back to the participants during the block of passive listening. We used both objective and subjective methods to ensure that the level of the playback during passive listening was identical to the level of voice feedback participants heard during active vocalization [Behroozmand and Larson, 2011; Chen et al., 2013b]. A RadioShack sound level meter (model 3300099) was used in the calibration procedure so that the intensity of the sounds fed to the insert earphones during passive listening was identical to that during active vocalization. As well, participants were asked to verify that the amplitude of voice loudness during passive listening and active vocalization was nearly identical.

Across two blocks, transistor-transistor logic (TTL) pulses were generated by a Max/MSP program to signal the onset of each pitch shift. The TTL pulses were also sent to the EEG recording system via an experimental synch DIN cable. The original and pitch-shifted voice signals as well as the TTL pulses were digitized at 10 kHz by a PowerLab A/D converter (model ML880, AD Instruments), and recorded onto another iMac using LabChart software (v.7.0 by AD Instruments).

Vocal Response Analysis

The magnitudes and latencies of vocal responses to FAF were measured using event-related averaging techniques [Li et al., 2013] in IGOR PRO software (v.6.0 by Wavemetrics Inc.). We first extracted voice F_0 contours in Hertz from the voice signals using Praat software [Boersma, 2001], and converted them to the cent scale using the following formula: $\text{cents} = 100 \times (12 \times \log_2(F_0/\text{reference}))$ [reference = 195.997 Hz (G4)]. The voice contours in cents were then segmented into epochs using a window of -200 to $+700$ ms relative to the onset of the pitch shift. A waterfall procedure was performed to visually inspect all individual segmented trials, and trials that were the result of vocal interruption or signal processing errors as well as those with large variability in the baseline period were regarded as bad trials and excluded from further analyses. Finally, 82% of trials that contained no artifacts were averaged to generate an overall response for each condition. The magnitude of a vocal response in cents was defined as the difference between the greatest F_0 value following the response onset and the mean of the baseline period. The response latency was defined as the time when the response exceeded 2 SDs above or below the baseline period following the stimulus onset. In addition, the SD of the baseline mean F_0 for the averaged response was calculated to index the amount of variability in the vocalization without feedback perturbations.

EEG Recording and Analysis

The EEG signals were recorded from each participant's scalp using a 64-electrode Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). Before the EEG recording, individual sensors were adjusted such that their impedance levels were less than 50 kΩ [Ferree et al., 2001]. The EEG signals were amplified by a Net Amps 300 amplifier (Electrical Geodesics Inc.) and recorded onto a Mac Pro computer using NetStation software (v.4.5, Electrical Geodesics Inc.). During the recording, the EEG signals from all channels were referenced to the vertex (Cz) and digitized at 1,000 Hz.

After data acquisition, NetStation software was used for the off-line analysis of the EEG signals. First, data were band-passed filtered with cut-off frequencies of 1–20 Hz and segmented into epochs from −200 to +500 ms relative to the onset of the pitch shift. Artifact detection was then carried out to exclude trials contaminated by excessive muscular activity, eye blinks, or eye movements. Any segment with voltage values exceeding ±55 μv of the moving average over an 80-ms window was rejected from further analyses. Individual electrodes that contained artifacts in more than 20% of the segments were rejected, and any file that contained more than 10 bad channels was excluded from the averaging procedure. Additionally, we visually inspected all trials to ensure that artifacts were appropriately rejected. On average, 79% of trials were retained for the following averaging procedure. Finally, all channels were re-referenced to the average of electrodes on each mastoid, and artifact-free trials were averaged and baseline-corrected to generate an overall response. The amplitudes and latencies of the N1 and P2 components were measured as the negative and positive peaks in the time windows of 80–180 and 160–280 ms after the onset of the pitch shift, respectively.

sLORERA Analysis

sLORETA was used to calculate the cortical distribution of current density for both the N1 and P2 components across task (active vocalization vs. passive listening) and group (individuals with PD vs. healthy controls). This method provides a single linear solution to the inverse problem of localization of cerebral sources based on a linear weighted sum of the scalp electric potentials [Pascual-Marqui, 2002]. Under the assumption that neighboring voxels should have maximally similar electrical activity [Fallgatter et al., 2003], sLORETA calculates the standardized current density of a dense grid of 6,239 voxels at 5 mm spatial resolution in the grey matter and the hippocampus of the MNI-reference brain. The accuracy of localization of possible underlying sources using sLORETA has been validated in the past studies using fMRI [Mulert et al., 2004], PET [Pizzagalli et al., 2004], and intra-cerebral recordings [Zumsteg et al., 2006]. sLORETA was computed based on the averaged ERPs for each subject using EEGLAB software (http://www.sccn.ucsd.edu/eeglab). The voxel-based sLORETA images were calculated using a realistic standardized head model [Fuchs et al., 2002] and the MNI152 template [Mazziotta et al., 2001] with the three-dimensional solution space restricted to cortical grey matter. In the present study, sLORETA images were computed at the 5 ms time windows of maximal global field power peaks within the N1 and P2 time windows. Voxel-by-voxel comparisons of the current density distributions across task and group were performed using EEGLAB's sLORETA voxelwise randomization tests (5,000 permutations) based on statistical non-parametric mapping, and corrected for multiple comparisons. The voxels with significant differences (for corrected $P < 0.05$) were specified in Montreal Neurological Institute (MNI) coordinates and labeled as Brodmann areas (BA) within the EEGLAB software.

Statistical Analyses

The magnitudes and latencies of the vocal and ERP responses to pitch-shifted voice auditory feedback across all the conditions were subjected to repeated-measures analyses of variance (RM-ANOVA) using SPSS (v.16.0). The magnitudes and latencies of vocal responses were analyzed using one-way RM-ANOVAs, in which group (individuals with PD vs. healthy controls) was the between-subject factor. The amplitudes and latencies of the N1-P2 complex were subjected to three-way RM-ANOVAs. Task (active vocalization vs. passive listening) and electrode (FC1, FC2, FCz, FC3, FC4, C1, C2, Cz, C3, C4) were within-subject factors, and group was the between-subject factor. These electrodes were chosen because cortical responses to pitch-shifted voice auditory feedback are most pronounced in the frontal and central electrodes [Chen et al., 2012; Hawco et al., 2009]. Any significant higher-order interactions led to subsidiary RM-ANOVAs, and post-hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons. Probability values were corrected using Greenhouse–Geisser for multiple degrees of freedom in the case of violations of the sphericity assumption. An alpha level of 0.05 was considered significant for all statistical analyses.

RESULTS

Behavioral Findings

Figure 1A shows the grand-averaged voice F_0 contours and mean magnitudes of vocal compensation for pitch-shifted auditory feedback as a function of group. As can be seen, individuals with PD (24 ± 13 cents) produced significantly larger magnitudes of vocal responses than healthy controls (15 ± 5 cents) ($F(1, 34) = 6.432$, $P = 0.016$). Regarding the response latencies, there was no significant difference between individuals with PD (96 ± 34 ms) and healthy controls (88 ± 27 ms) ($F(1, 34) = 0.603$, $P = 0.443$).

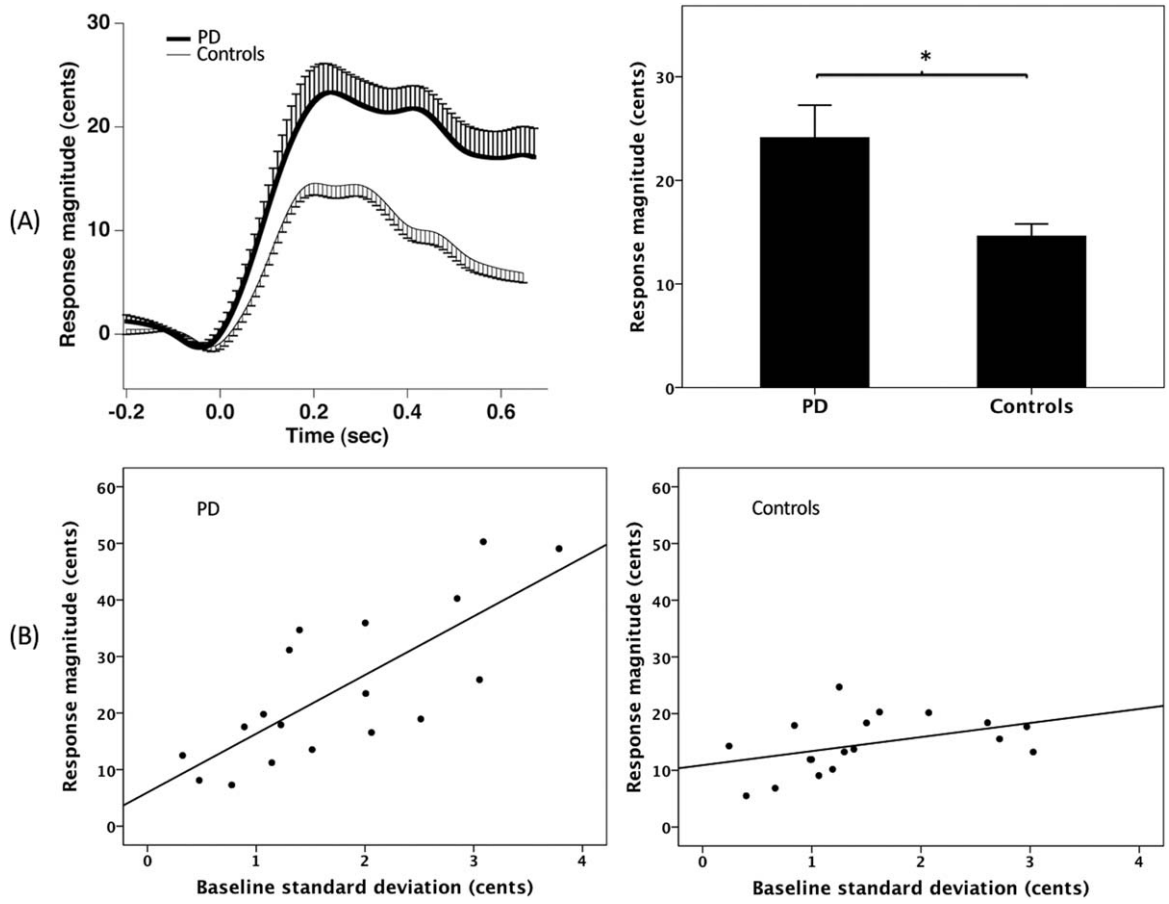

Figure 1.

(A) Grand-averaged voice F_0 contours (left) and mean magnitudes of vocal responses to pitch-shifted voice auditory feedback for individuals with PD and healthy controls. Vertical bars represent the standard errors of the averaged contours, and the asterisk indicates the significant differences in the vocal response magnitudes between the two groups. (B) Correlations between the magnitudes of vocal responses to pitch-shifted voice auditory feedback and the standard deviations (SDs) of the baseline voice F_0 for individuals with PD (left) and healthy controls (right).

We also performed regression analyses to investigate the relationship between the magnitudes of vocal compensations for pitch feedback errors and the variability of the baseline voice while hearing normal feedback [Chen et al., 2013a; Scheerer and Jones, 2012]. The results revealed a significant positive correlation between the magnitudes of vocal responses and the SDs of the baseline F_0 for individuals with PD ($F(1, 16) = 23.027$, $P < 0.001$), whereas the correlation between these two variables did not reach significance for healthy controls ($F(1, 16) = 3.476$, $P = 0.081$) (see Fig. 1B).

ERP Findings

Figure 2 shows the grand-averaged ERP waveforms and topographical distributions of N1 and P2 components in response to pitch-shifted auditory feedback during active vocalization (red solid lines) and passive listening (blue solid lines) for individuals with PD and healthy controls. Figure 3 shows the mean amplitudes of N1 (A) and P2 (B) components during active vocalization (black bars) and passive listening (blank bars) for individuals with PD and healthy controls.

A three-way RM-ANOVA conducted on the N1 amplitudes revealed a significant main effect of task ($F(1, 34) = 17.146$, $P < 0.001$), showing that both individuals with PD and healthy controls produced smaller N1 responses (less negative) during active vocalization (-1.79 ± 1.52 μV) relative to passive listening (-2.69 ± 1.88μV) (see Figs. 2 and 3A). The main effect of electrode ($F(9, 306) = 6.812$, $P < 0.001$) was also significant. N1 responses recorded at electrode C3 were less negative than the N1 amplitudes recorded from the other electrodes. However, the main

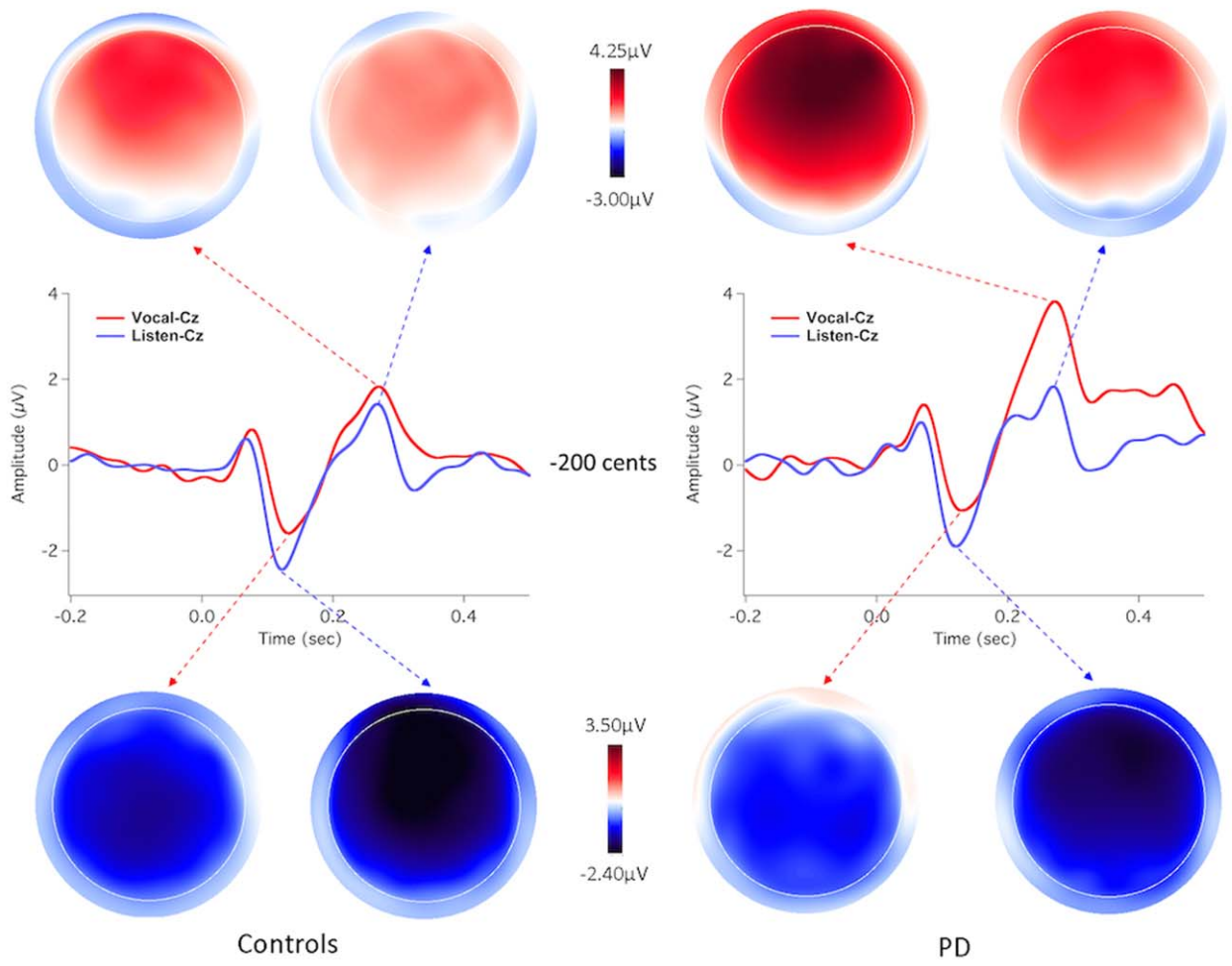

Figure 2.
Grand-averaged ERP waveforms at Cz and the topographical distributions of N1 (bottom) and P2 (top) amplitudes in response to pitch-shifted voice auditory feedback for healthy controls (left) and individuals with PD (right) during active vocalization (red solid lines) and passive listening (blue solid lines), respectively. [Color figure can be viewed at wileyonlinelibrary.com]

effect of group ($F(1, 34) = 0.185$, $P = 0.669$; PD: -2.14 ± 2.12 μV; controls: -2.34 ± 1.32 μV) and the interactions between the factors ($P > 0.05$) did not reach significance.

Regarding the N1 latencies, the passive listening condition (128 ± 19 ms) elicited faster N1 responses than the active vocalization condition (140 ± 23 ms) ($F(1, 34) = 9.662$, $P = 0.004$). However, main effects of electrode ($F(9, 306) = 0.799$, $P = 0.477$) and group ($F(1, 34) = 0.182$, $P = 0.672$), as well as the interactions between these factors did not reach significance ($P > 0.05$).

A three-way RM-ANOVA conducted on the P2 amplitudes revealed a main effect of electrode ($F(9, 306) = 17.794$, $P < 0.001$), indicating larger P2 amplitudes at frontal electrodes relative to central electrodes. Significant systematic changes of P2 amplitudes were also observed as a function task ($F(1, 34) = 21.425$, $P < 0.001$) and group ($F(1, 34) = 13.008$, $P = 0.001$), but there was a significant interaction between task and group ($F(1, 34) = 7.306$, $P = 0.011$) (see Fig. 3B). Follow-up analyses showed that active vocalization (4.29 ± 1.95 μV) elicited significantly larger P2 amplitudes than passive listening (2.33 ± 0.98 μV) ($F(1, 17) = 30.645$, $P < 0.001$) for the PD group, whereas the main effect of task did not reach significance for the control group ($F(1, 17) = 1.651$, $P = 0.216$) (active vocalization: 2.17 ± 1.59 μV; passive listening: 1.65 ± 1.22 μV). In addition, individuals with PD produced significantly larger P2 amplitudes than healthy controls during active vocalization ($F(1, 34) = 13.838$, $P = 0.001$), but the groups did not significantly differ during passive listening ($F(1, 34) = 3.859$, $P = 0.058$).

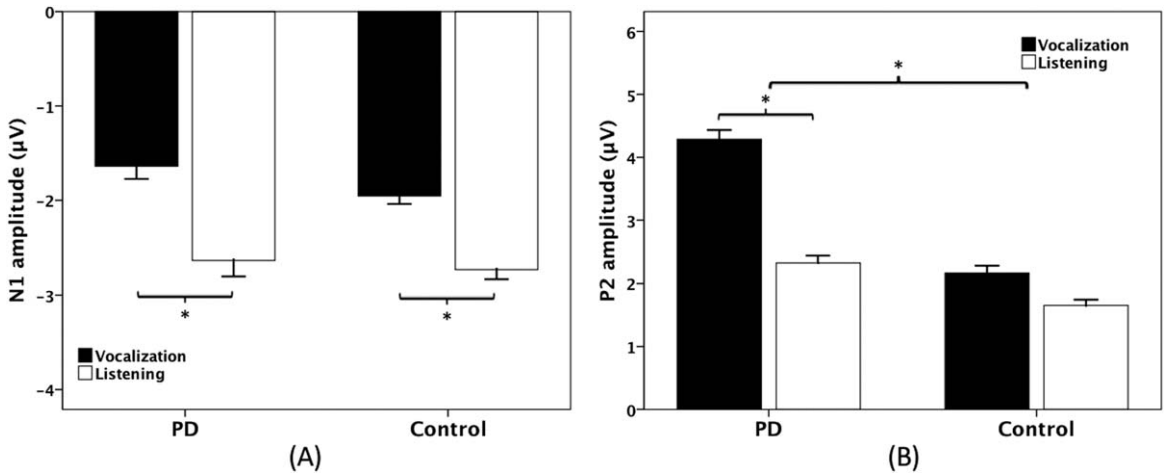

Figure 3.

T-bar plots of mean N1 (A) and P2 (B) amplitudes in response to pitch-shifted voice auditory feedback during active vocalization (black bars) and passive listening (blank bars) for individuals with PD and healthy controls.

P2 latencies did not differ as a function of task ($F(1, 34) = 0.803$, $P = 0.376$), electrode ($F(9, 306) = 0.701$, $P = 0.528$), or group ($F(1, 34) = 0.308$, $P = 0.582$). However, there was a marginally significant interaction between task and group ($F(1, 34) = 3.810$, $P = 0.059$); significantly longer P2 latencies were elicited by active vocalization (270 ± 16 ms) as compared with passive listening (259 ± 24 ms) for the PD group ($F(1, 17) = 5.084$, $P = 0.038$). The main effect of task, however, did not reach significance for the control group ($F(1, 17) = 0.463$, $P = 0.505$) (259 ± 26 ms vs. 263 ± 19 ms).

sLORETA Findings

Figure 4 shows estimated current density source maps projected onto the cortical layer of the realistic standardized head model (top) and the MNI 152 template (bottom), which depict the statistical differences (Log of ratio of averages) of the relative current densities during the active vocalization condition between individuals with PD and healthy controls for the P2 analysis window. The squared magnitude of the current density is color coded to indicate the level of significant difference. Table I lists the MNI coordinates and corresponding brain regions associated with current density maxima. As can be seen, significant sources were mainly located in the left hemisphere including the superior frontal gyrus (SFG) (BA 10, $P < 0.01$), PMC (BA 6, $P < 0.01$), IFG (BA 45, $P < 0.01$), IPL (BA 40, $P = 0.01$), and STG (BA 22, $P = 0.016$). In all these areas, individuals with PD showed enhanced activation relative to healthy controls. Figure 5 and Table II illustrate results of estimated current density source maps, which show the statistical differences between active vocalization and passive listening for individuals with PD during the P2 analysis window. Significant sources were located in the IFG (BA 45, BA 47, $P < 0.01$), precentral gyrus (PrCG) (BA 6, $P < 0.01$), postcentral gyrus (PoCG) (BA 2, $P = 0.012$), and middle temporal gryus (MTG) (BA 21, $P = 0.018$) (see Table II). In all these areas, active vocalization elicited enhanced activation relative to passive listening. Although active vocalization elicited significantly less negative N1 responses than passive listening for both individuals with PD and healthy controls, different levels of current density across these task conditions did not reach significance and therefore are not illustrated.

DISCUSSION

The present study examined the effects of PD on the neural processing that underlies auditory–motor integration for voice control by comparing the behavioral and cortical responses to FAF in individuals with PD to the responses observed in healthy controls. Behaviorally, individuals with PD produced significantly larger vocal responses than healthy controls. In addition, the magnitude of the vocal compensations produced by individuals with PD was positively correlated with the variability of their baseline voice F_0. This correlation did not exist for the healthy controls. Differences in cortical activity were also observed between the two groups: individuals with PD produced significantly larger P2 responses than healthy controls during active vocalization, and this group difference was statistically significant in the SFG, PMC, IFG, IPL, and STG. When passively listening to the playback of their pitch-shifted voice, however, the groups did not differ in their cortical responses to FAF. Individuals with PD produced significantly larger P2 responses during active vocalization compared with passive listening, but healthy controls did not. This effect was due to left-

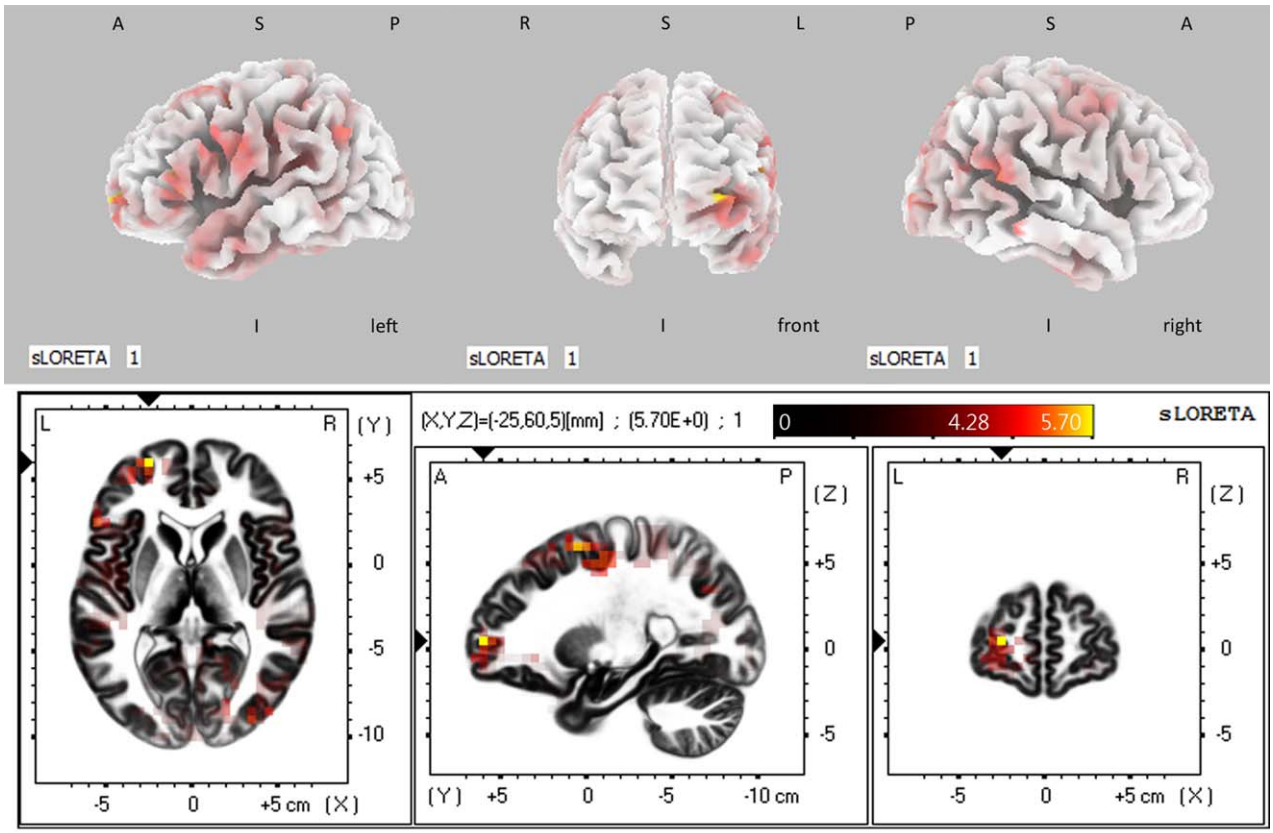

Figure 4.

Maximum sLORETA-activations (mean current source density in μA/mm2) of brain activity between individuals with PD and healthy controls in the P2 time-range. The results have been projected onto the cortical layer of the realistic standardized head model and the MNI 152 template. The squared magnitude of the current density is color coded to indicate the level of significant difference between individuals with PD and healthy controls. Abbreviations: A, anterior; P, posterior; S, superior; I, inferior; L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

lateralized enhanced activity in the IFG, PrCG, PoCG, and MTG. In addition, N1 responses did not differ between the two groups, but active vocalization elicited significantly smaller N1 responses than passive listening for both individuals with PD and healthy controls. These results demonstrate that the neural processes that support auditory–motor integration during voice control are altered by PD and that these abnormalities may be related to their deficits in both perceiving and correcting for feedback errors during vocal pitch regulation.

As expected, the behavioral results revealed that individuals with PD produced significantly larger vocal responses to FAF than healthy controls, which is consistent with other behavioral studies [Chen et al., 2013a; Liu et al., 2012]. We also replicated the findings reported by Chen et al. [2013a] that showed a significant positive correlation between the magnitude of vocal responses and the variability of the baseline voice F_0 for individuals with PD. Together with the results of the present study, these findings provide evidence that PD interferes with the mechanisms that allow for the execution of the vocal compensations necessary to stabilize vocal production when pitch errors are detected through auditory feedback.

The observation that the increased variability in voice F_0 production, an early symptom of PD [Harel et al., 2004], is associated with larger magnitudes of vocal compensation for pitch-shifted auditory feedback suggests that PD causes the speech motor system to overvalue auditory feedback during vocalization [Chen et al., 2013a; Liu et al., 2012]. According to the DIVA model [Guenther, 2006], speech production relies on previously learned motor commands that are executed under feedforward control, and sensory feedback (auditory and somatosensory) is monitored to detect and correct for any deviations from the intended speech output. The BG-SMA circuit, which is thought to play a primary role in feedforward control [Cunnington et al., 1996; Nixon and Passingham, 1998], is compromised by the loss of dopaminergic neurons in the

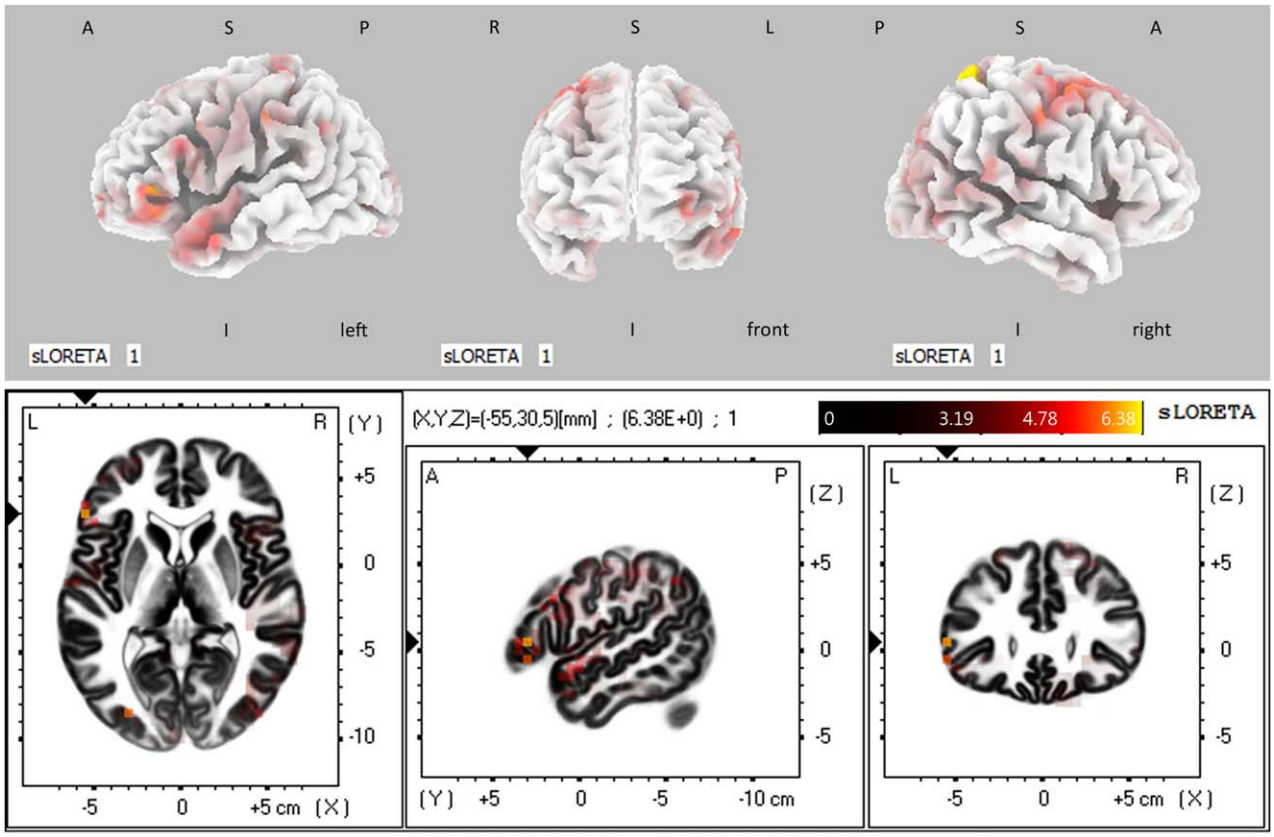

Figure 5.

Maximum sLORETA-activations (mean current source density in μA/mm2) of brain activity for individuals with PD between active vocalization and passive listening in the P2 time-range. The results have been projected onto the cortical layer of the realistic standardized head model and the MNI 152 template. The squared magnitude of the current density is color coded to indicate the level of significant difference between active vocalization and passive listening. Abbreviations: A, anterior; P, posterior; S, superior; I, inferior; L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

BG in individuals with PD [Haslinger et al., 2001]. Thus, the impaired connection between the BG and SMA leads to dysfunctions in feedforward control [Alm, 2004]. Also, Hammer and Barlow [2010] reported deficits in laryngeal somatosensory function in individuals with PD, suggesting that PD causes an impaired ability to integrate somatosensory information into the vocal motor systems. On the other hand, the fact that individuals with PD often overestimate the loudness of their voice volume or vocal effort [Fox et al., 2002; Ho et al., 2000] suggests that individuals with PD may have intensified experiences when perceiving self-produced speech. In the presence of dysfunctions in the neural systems that support feedforward control and/or dysfunctions in the processing of somatosensory feedback, therefore, individuals with PD may place greater weight on auditory feedback such that any discrepancies between expected and actual auditory feedback elicit larger vocal responses in individuals with PD than in healthy individuals.

The fact that individuals with PD produced larger P2 responses than did healthy controls in the present study also provides supportive evidence for this point. According to the internal forward model theory [Blakemore et al., 1998; Wolpert et al., 1995], the sensory consequences of an action can be predicted based on an efference copy of the motor commands [Von Holst, 1954]. During speech production, a subtractive comparison of the efference copy with the actual feedback enables speakers to detect feedback errors, and generate a corrective response when a discrepancy results from this comparison [Chang et al., 2013]. Source estimation analyses of the P2 responses during active vocalization revealed increased activity in the STG (BA 22) in individuals with PD, which suggests that PD may lead to an overestimation of the size of pitch feedback errors during the online monitoring of speech production. This intensified perception of actual feedback for individuals with PD may result in a larger discrepancy than that experienced by healthy individuals, which in the

TABLE I. sLORETA *t* statistics for maximum activations obtained from comparison between individuals with PD and healthy controls during active vocalization in the P2 time window (MNI coordinates)

Condition	BA	Brain region	*t*-value	X	Y	Z
PD vs. controls	10	Superior Temporal Gyrus	5.70	−25	58	2
	6	Middle Frontal Gyrus	5.45	−25	8	55
	45	Inferior Frontal Gyrus	5.16	−50	25	17
	40	Inferior Parietal Lobule	5.02	−40	−56	44
	22	Superior Temporal Gyrus	4.73	64	−43	16

Displayed are *t*-values for current density maxima, threshold for significance at a *t* value of 4.05 ($P < 0.05$, corrected for multiple comparisons).

present study led to the larger cortical responses to FAF during active vocalization, according to the forward model hypothesis. Considering that activity in the STG is positively correlated with the magnitude of vocal compensations for FAF [Behroozmand et al., 2015; Chang et al., 2013], it makes sense that individuals with PD showed increased activation in the STG and that they produced larger vocal compensations than healthy controls. Note that individuals with PD and healthy controls did not differ significantly in their cortical responses to FAF during passive listening. These findings can account for the clinical observation that individuals with PD often overestimate their vocal efforts while their receptive listening is normal [Fox et al., 2002], and lends support for the idea that individuals with PD have dysfunctions in the perception of their auditory feedback during vocal production.

The source estimation approach revealed left-lateralized enhanced activity in brain regions including the STG (BA 22), PMC (BA 6), IFG (BA 45), IPL (BA 40), and SFG (BA 10) (Fig. 4 and Table I) that contributed to the larger P2 responses produced by individuals with PD in comparison to healthy controls. This enhanced activity in the individuals with PD suggests that the loss of dopaminergic neurons in the BG alters auditory–motor integration for voice control in PD at the cortical level. A number of other neuroimaging studies have demonstrated activation of the STG, PMC, and IFG in the detection and/or correction of feedback errors during vocal pitch regulation [Behroozmand et al., 2015; Chang et al., 2013; Flagmeier et al., 2014; Greenlee et al., 2013; Kort et al., 2014; Parkinson et al., 2012; Tourville et al., 2008]. In particular, activity in the PMC and STG is predictive of the magnitude of vocal compensation for pitch feedback errors [Behroozmand et al., 2015; Chang et al., 2013]. Also Flagmeier et al. [2014] reported effective connectivity between IFG and both STG and PMC when participants heard pitch perturbations in their voice auditory feedback, which suggests that the IFG plays a critical role in the processing of sensorimotor information during vocal production [Tourville et al., 2008]. The present study, in conjunction with previous studies, provides further evidence for the involvement of the STG, PMC, and IFG in the auditory–motor integration for voice F_0 control.

The enhanced activity in the IPL (BA 40) and the SFG (BA 10, or anterior prefrontal cortex) that was observed for individuals with PD when compared with healthy controls during active vocalization has not been reported in previous studies of sensorimotor integration for voice control. However, recruitment of the IPL has been observed when participants were exposed to delayed auditory feedback [Hashimoto and Sakai, 2003], and when participants adapted their motor commands to new sensorimotor conditions [Shum et al., 2011]. In the dual-stream model proposed by Hickok and his colleagues, the Sylvian fissure at the parieto-temporal boundary (Spt) located in the IPL serves as an interface that performs a coordinate transformation between auditory and motor representations [Hickok et al., 2011; Hickok and Poeppel, 2007]. As well,

TABLE II. sLORETA t statistics for maximum activations obtained from comparison between active vocalization and passive listening for individuals with PD in the P2 time window (MNI coordinates)

Condition	BA	Brain region	*t*-value	X	Y	Z
Vocalization vs. listening	45	Inferior Frontal Gyrus	6.38	−54	29	3
	47	Inferior Frontal Gyrus	5.90	−54	29	−6
	2	Postcentral Gyrus	6.25	−30	−36	62
	6	Precentral Gyrus	6.03	45	−2	55
	21	Middle Temporal Gyrus	5.64	−59	−1	−17

Displayed are *t*-values for current density maxima, threshold for significance at a *t* value of 4.96 ($P < 0.05$, corrected for multiple comparisons).

Rauschecker and Scott [2009] propose in their dual auditory processing model that the IPL may be a location where feedforward signals from IFG and PMC to the IPL and posterior superior temporal (pST) region (or planum temporale) are compared with feedback signals that come from the pST during speech processing. Thus, in the current study, enhanced activity of the IPL for individuals with PD may reflect increased interactions between auditory and motor areas during active vocalization compared with healthy controls. As for the SFG, studies have demonstrated its role in generating internally produced events [Ramnani and Owen, 2004] and monitoring the online status of an ongoing task using feedback [Koechlin and Hyafil, 2007]. Thus, it is possible that enhanced activation of the SFG indicate that, as compared with healthy controls, individuals with PD require more prefrontal resources to monitor the dynamic state of their auditory–vocal system for the online control of vocal production.

It is noteworthy that the group differences in the current densities were mainly lateralized to the left hemisphere. This finding is in line with one fMRI study that showed increased activity in the left IFG, PMC, and auditory cortex during an overt reading task for individuals with PD compared with healthy controls [Arnold et al., 2014]. Also in two PET studies that investigated the neural correlates of vocal therapy for the symptoms of PD [Liotti et al., 2003; Narayana et al., 2010], there was left-lateralized brain activation when individuals with PD read a paragraph before receiving the treatment, and a rightward shift of the brain activation in the DLFPC, PMC, and auditory cortices after receiving the treatment. These studies suggest that the left-lateralized neural processes that support auditory–motor integration for voice control may be impaired in individuals with PD. Other studies, however, have reported that PD causes abnormal right hemisphere lateralization during speech production [Rektorova et al., 2007, 2012]. For example, individuals with PD exhibited increased connectivity between PAG and BG, posterior STG, and IPL in the right hemisphere compared with healthy controls [Rektorova et al., 2012]. Further studies, therefore, should be conducted to verify our findings.

As expected, active vocalization elicited significantly larger P2 responses to FAF than passive listening for individuals with PD. This finding is consistent with previous studies in animals and humans that showed a similar vocalization-induced enhancement of cortical responses [Behroozmand et al., 2009, 2011, 2015; Chang et al., 2013; Chen et al., 2013b; Eliades and Wang, 2008; Greenlee et al., 2013; Liu et al., 2010]. The comparison of the P2 source estimations revealed that the vocalization-induced enhancement observed in individuals with PD was due to enhanced activity in the IFG (BA 45), PrCG (BA 6), PoCG (BA 2), and MTG (BA 21) (Fig. 5 and Table II). This finding is consistent with one recent fMRI study that showed increased activation of PrCG, SMA, PoCG, IFG, and insula during active vocalization vs. passive listening [Behroozmand et al., 2015]. Results from two ECoG studies have also shown vocalization-induced enhancement of neural responses to FAF within the posterior STG and/or the ventral portion of the PrCG [Chang et al., 2013; Greenlee et al., 2013]. Together with the present study, this converging evidence suggests that the abnormalities of speech motor control associated with PD is not caused by dysfunctions in the sensory systems alone, but by impairments in the neural networks that are involved in the integration of sensory and motor information during vocalization.

It is unexpected that enhancement of P2 responses during active vocalization relative to passive listening was not observed for healthy controls, and that active vocalization elicited suppressed N1 responses relative to passive listening for both individuals with PD and healthy controls. These findings are in contrast with previous research that showed enhanced P2 responses, but intact N1 responses during active vocalization relative to passive listening [Behroozmand et al., 2009, 2011; Chen et al., 2013b]. Note that those studies were limited to young adults, while the participants in the present study were elderly adults. There has been much neural evidence for the age-related decline in processing and producing speech. For example, as compared with young healthy controls, elderly adults exhibited decreased activity in the sensory cortical areas and amplitudes of N1/P2 components when exposed to speech sounds or pure tones [Golob and Starr, 2000; Ostroff et al., 2003; Wong et al., 2009] or during overt speech production [Soros et al., 2011; Tremblay et al., 2013]. It is thus likely that the inconsistency between the present study and previous studies might be related to the age-related decline in speech perception and production. However, because of the lack of knowledge about the effect of age on the cortical processing of auditory feedback during vocal motor control and N1 and P2 responses to FAF, this explanation remains speculative. Nevertheless, the different patterns of vocalization-induced modulation of cortical responses to FAF that we observed between individuals with PD and healthy controls provides further evidence that PD impairs the integration of the auditory and motor systems during vocal pitch regulation.

Despite the superior temporal resolution of EEG, a major drawback of the present study is that source estimation of N1/P2 responses was calculated using 64 electrodes and a realistic standardized head model. The use of high-density EEG recordings (128 or 256 electrodes) and a realistic individual head model from MRI images will significantly improve the accuracy of source localization. The limitation in the spatial resolution of EEG restricts our examination of cortical structures that are involved in the feedback-based processing of vocal pitch regulation. However, the present study paves the way for further research that use the source-localized EEG technique for studying the spatio-temporal pattern of brain activity during auditory-motor integration for voice control in individuals with PD.

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